

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 03 April 2001 (03.04.01)	
International application No. PCT/GB00/02584	Applicant's or agent's file reference RRS/7237INT
International filing date (day/month/year) 05 July 2000 (05.07.00)	Priority date (day/month/year) 16 July 1999 (16.07.99)
Applicant COOPER, John, Joseph	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:13 February 2001 (13.02.01)☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Pascal Piriou
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/02584

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C01F11/46 A61L27/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C01F A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 197732 Derwent Publications Ltd., London, GB; Class E33, AN 1977-56914Y XP002151853 & JP 52 027120 B (LION FAT & OIL CO LTD), 18 July 1977 (1977-07-18) abstract	1-7, 12-34, 45-47
Y		8-11, 35-44
Y	EP 0 370 703 A (UNITED STATES GYPSUM CO) 30 May 1990 (1990-05-30) claims 19,23-25	8-11
Y	US 4 360 386 A (BOUNINI LARBI) 23 November 1982 (1982-11-23) the whole document	35-44
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

2 November 2000

Date of mailing of the international search report

15/11/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3018

Authorized officer

Zalm, W

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 00/02584

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 281 265 A (LIU SUNG-TSUEN) 25 January 1994 (1994-01-25) the whole document	2
A	US 5 756 127 A (GRISONI BERNARD F ET AL) 26 May 1998 (1998-05-26) the whole document	2

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- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
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Fax: (+31-70) 340-3016

Authorized officer

Zalm, W

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/02584

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Application No

PCT/GB 00/02584

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
JP 52027120	B	18-07-1977	NONE	
EP 0370703	A	30-05-1990	AT 117972 T	15-02-1995
			AU 637078 B	20-05-1993
			AU 4828690 A	12-06-1990
			BR 8907778 A	22-10-1991
			CA 2003046 A,C	18-05-1990
			DD 294458 A	02-10-1991
			DE 68921009 D	16-03-1995
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			DK 90191 A	02-07-1991
			EG 20287 A	30-07-1998
			EP 0444153 A	04-09-1991
			ES 2072911 T	01-08-1995
			FI 100100 B	30-09-1997
			HU 58665 A	30-03-1992
			HU 216298 B	28-06-1999
			IE 68456 B	26-06-1996
			JP 4501703 T	26-03-1992
			KR 9705867 B	21-04-1997
			LT 1746 A,B	25-07-1995
			LV 11025 A	22-02-1996
			LV 11025 B	20-06-1996
			MD 950087 A	28-06-1996
			NO 911935 A	16-05-1991
			RU 2101252 C	10-01-1998
			WO 9005709 A	31-05-1990
			US 5320677 A	14-06-1994
US 4360386	A	23-11-1982	CA 1163417 A	13-03-1984
			DE 3239737 A	01-12-1983
			DE 3239737 T	01-12-1983
			EP 0077373 A	27-04-1983
			GB 2101107 A,B	12-01-1983
			JP 58500523 T	07-04-1983
			WO 8203379 A	14-10-1982
US 5281265	A	25-01-1994	NONE	
US 5756127	A	26-05-1998	NONE	

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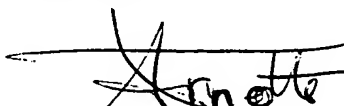

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RRS/7237INT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB 00/ 02584	International filing date (day/month/year) 05/07/2000	Priority date (day/month/year) 16/07/1999
International Patent Classification (IPC) or national classification and IPC C01F11/46		
Applicant BIOCOMPOSITES LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This **REPORT** consists of a total of 5 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consists of a total of 2 sheets.

3. This report contains indications relating to the following items:
- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 13/02/2001	Date of completion of this report 19. 09. 01
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer  

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

I. Basis of the report

1. This report has been drawn up on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*

☒ the international application as originally filed

☐ the description, pages , as originally filed
 pages , filed with the demand
 pages , filed with the letter of

☐ the claims, Nos. , as originally filed
 Nos. , as amended under Article 19
 Nos. , filed with the demand
 Nos. , filed with the letter of

☐ the drawings, sheets / fig. , as originally filed
 sheets / fig. , filed with the demand
 sheets / fig. , filed with the letter of

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.
☐ the drawings, sheets / fig.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2 (c)).

4. Additional observations, if necessary:

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty	Claims	1-46	YES
	Claims		NO
Inventive Step	Claims	1-46	YES
	Claims		NO
Industrial Applicability	Claims	1-46	YES
	Claims		NO

2. Citations and Explanations

1. Claim 1 relates to a method of producing a surgical grade calcium sulphate and includes the steps of forming a high purity synthetic calcium sulphate dihydrate having a high surface area, fully dehydrating this material to form anhydrous calcium sulphate and fully rehydrating (at room temperature) this material to give a low surface area calcium sulphate dihydrate for use as a bone void filler.

It is important that surgical grade calcium sulphate has high levels of purity and consistency and this is best achieved and controlled by employing as a source material, a synthetically prepared calcium sulphate dihydrate rather than a commercially mined gypsum mineral. However, synthetically prepared calcium sulphate dihydrate generally has a high surface area and small particle size, making it unsuitable for use directly as a bone graft (bone void filler) material.

To overcome this problem, the dehydration and subsequent rehydration steps as disclosed in claim 1, result in the production of a coarse textured low surface area calcium sulphate dihydrate from the synthetically prepared fine powdered high surface area calcium sulphate dihydrate. This coarse textured material is more suitable for processing into a bone void filler material.

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

2. D1 - WPI XP 002151853

D1 describes a method of forming gypsum in which a commercially available gypsum powder having a particle size of approximately $100\mu\text{m}$ is partially dehydrated to produce calcium sulphate hemihydrate. It is then rehydrated under chilled conditions in a minimum quantity of water, resulting in a gypsum with a smaller particle size, less than $10\mu\text{m}$, and hence large surface area. The resulting material is used as a cement additive, plasterboard, a filler, sizing agent, etc.

3. D2 - EP 0370703

D2 describes a method of forming a composite material which comprises heating a mixture of gypsum and cellulosic particles in an autoclave to give a calcium sulphate hemihydrate/cellulosic mixture. This is then dewatered and dried to provide a composite material in which calcium sulphate crystals are interlocked with the cellulosic particles. The composite material has particular application for use in wallboards.

4. D3 - US 4360386

D3 describes a process in which beta calcium sulphate hemihydrate having a generally high water demand (high consistency) is treated with a solution of "solubilising agent" preferably in an impacting blender. This provides a calcium sulphate of reduced water demand (consistency) to be used for gypsum board.

5. D1 to D3 all describe methods for producing gypsum for building applications and are therefore remote from the present invention which is clearly directed to a method of producing surgical grade calcium sulphate. Further D1 which appears to be the most relevant prior art, employs a commercially available gypsum powder and thus teaches further away from the present invention in which the gypsums is synthetically prepared.

6. Therefore, claims 1-46 are regarded as being novel and inventive over D1-D3.

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. Claim 2 should be reformulated as a use claim.
2. Claim 47 is not acceptable because it does not relate to a specified product; in other words, the subject-matter of claim 47 is so vague that said claim is not acceptable as it stands.

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference RRS/7237INT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 00/ 02584	International filing date (day/month/year) 05/07/2000	(Earliest) Priority Date (day/month/year) 16/07/1999
Applicant BIOCOMPOSITES LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of Invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

METHOD OF PRODUCING SURGICAL GRADE CALCIUM SULPHATE

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/02584

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C01F11/46 A61L27/02

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Authorized officer

Zalm, W

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			JP 58500523 T	07-04-1983
			WO 8203379 A	14-10-1982
US 5281265	A	25-01-1994	NONE	
US 5756127	A	26-05-1998	NONE	

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(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
25 January 2001 (25.01.2001)

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(10) International Publication Number
WO 01/05706 A1

- (51) International Patent Classification⁷: C01F 11/46, A61L 27/02
- (21) International Application Number: PCT/GB00/02584
- (22) International Filing Date: 5 July 2000 (05.07.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
9916601.9 16 July 1999 (16.07.1999) GB
- (71) Applicant (for all designated States except US): BIO-COMPOSITES LIMITED [GB/GB]; Etruscan Street, Etruria, Stoke-on-Trent, Staffordshire ST1 5PQ (GB).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): COOPER, John, Joseph [GB/GB]; Biocomposites Limited, Etruscan Street, Etruria, Stoke-on-Trent, Staffordshire ST1 5PQ (GB).
- (74) Agent: SALES, Robert, Reginald; Swindell & Pearson, 48 Friar Gate, Derby DE1 1GY (GB).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:**
- With international search report.
 - Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: METHOD OF PRODUCING SURGICAL GRADE CALCIUM SULPHATE

(57) Abstract: A method of producing surgical grade calcium sulphate suitable for use as resorbable osteoconductive bone void filler material. The method comprising forming an initial calcium sulphate di-hydrate from synthetic constituents; dehydrating the initial calcium sulphate di-hydrate to form calcium sulphate anhydrite; and subsequently rehydrating the calcium sulphate anhydrite and allowing subsequent calcium sulphate di-hydrate to crystallise out.

WO 01/05706 A1

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METHOD OF PRODUCING SURGICAL GRADE CALCIUM SULPHATE

This invention concerns a method of producing surgical grade calcium sulphate and particularly but not exclusively a method of producing a resorbable osteoconductive bone void filler material.

Plaster of paris (hemi-hydrate calcium sulphate) is known to be suitable for use as a filler for bone defects. This material provides a number of required characteristics and does not produce any significant undesirable reaction within a body. Traditionally plaster of paris is produced from naturally occurring gypsum. This often has associated undesirable impurities. For medical applications and particularly for implantation high purity materials are obviously needed. Whilst it is possible for calcium sulphate to be produced synthetically, conventional techniques produce a material which has a high surface area which thus has a high water demand and therefore produces a low strength material when set. Such set material has a high dissolution rate and too short a residence time when implanted.

Plaster of paris, or more accurately calcium sulphate, has two modes of use as a bone filler. The first is in the di-hydrate form, usually as pellets which can be placed in a bone void. The second is as a hemi-hydrate powder which can be made up with water into a paste, which paste is mouldable to a required shape. Such materials are usable in the fields of orthopaedic, dental and maxillofacial surgery. Hemi-hydrate calcium sulphate has two forms. The first α is produced by hydrothermal treatment of the di-hydrate. The second β is produced by dry heat calcination. This latter form tends to have a low density, a higher water demand and therefore a lower strength and a faster dissolution rate than the α form.

According to the present invention there is provided a method of producing surgical grade calcium sulphate, the method comprising forming an initial calcium sulphate di-hydrate from synthetic constituents; dehydrating the initial calcium sulphate di-hydrate to form calcium sulphate anhydrite; and

subsequently rehydrating the calcium sulphate anhydrite and allowing subsequent calcium sulphate di-hydrate to crystallise out.

The subsequent di-hydrate may be used as a solid material bone filler and may be formed into pellets. The crystallised subsequent calcium sulphate di-hydrate may be ground prior to forming into pellets.

Alternatively, the subsequent calcium sulphate di-hydrate may be calcined to form calcium sulphate hemi-hydrate, which material can be mixed with water or a salt solution to form a settable paste.

The calcining may be hydrothermal to form α calcium sulphate hemi-hydrate, and may be carried out in an autoclave. The calcining may be carried out at a pressure of 1-6 bar, and desirably 2-3 bar. The calcining is preferably carried out for a half to five hours, and desirably one to two hours.

Alternatively, the calcining may be carried out in dry heat conditions. The calcining may be carried out at a temperature of 70 - 200°C and desirably at 150 - 175°C, and for a period of a half to six hours and desirably one to two hours.

Following calcining, the calcium sulphate hemi-hydrate is preferably ground to a powder, and desirably with a particle size of less than 150 microns.

The initial calcium sulphate di-hydrate may be formed by mixing soluble calcium and sulphate salts such that calcium sulphate precipitates out. The di-hydrate thus formed may be washed, and subsequently filtered, crushed and/or dried.

The calcium salt may be a chloride or nitrate. The sulphate may be a sodium, potassium or ammonium salt. The calcium and sulphate salts are preferably provided in a substantially equal molecular ratio.

Alternatively the initial calcium sulphate di-hydrate may be formed from neutralising lime with sulphuric acid.

The dehydration of the initial calcium sulphate di-hydrate preferably takes place within a temperature range 110 - 350° and desirably at less than 300°C, to form soluble calcium sulphate anhydrite. Alternatively the dehydration may take place at a temperature above 350°C to form insoluble anhydrite.

The dehydration of the initial calcium sulphate di-hydrate by the application of heat may take place in an open container, or in a closed container, or hydrothermally in the presence of steam.

The rehydration of the calcium sulphate anhydrite preferably takes place immediately following dehydration. The calcium sulphate anhydrite is preferably fully immersed in water or an aqueous solution for rehydration.

The rehydration may take place in water or a dilute salt solution. The salt solution may comprise succinic acid or a potassium sulphate solution, with a concentration of less than 1% and desirably substantially 0.1%.

Finely powdered calcium sulphate di-hydrate may be added to be present during rehydration such that the powdered calcium sulphate acts as crystal seeds, and the addition may be in the order of 5g per litre of water. For soluble anhydrite the rehydration preferably takes less than five days, and for insoluble anhydrite preferably more than five days.

The subsequent calcium sulphate di-hydrate is preferably dried following crystallisation. Alternatively, if it is to be autoclaved to form α hemi-hydrate it may be held in a damp condition.

Examples of the present invention will now be described by way of example only.

Example 1

4 moles of analytical grade potassium sulphate were dissolved in 2 l of deionised water. The resulting solution was added to a solution of 4 moles calcium nitrate in 2 l of deionised water. The precipitate so formed was washed free of all nitrate and filtered on a Buchner Funnel followed by a further wash on filter with 100ml of deionised water. The resultant filter cake was dried at 40°C. Its BET SSA (specific surface area measurement) was determined as 0.61 m²/gm.

500 gms of this calcium sulphate di-hydrate filter cake were lightly crushed, put into a 2 l borosilicate glass beaker, and placed in an oven at 200°C for 24 hours. On removal from the oven, 500 mls of deionised water - were added immediately to the beaker ensuring that all of the powder was immersed. This was allowed to soak for a period of 3 days, and then all supernatant liquid was drained away.

The resulting di-hydrate had a BET SSA of 0.06m²/gm. This coarse textured, granular, recrystallised di-hydrate was now placed in a stainless steel tray and autoclaved at 2.5 bar for a period of 2 hours. The α hemi-hydrate so formed was dried at 110°C for half hour prior to crushing in a pestle and mortar to pass a 150 micron mesh sieve.

The material so formed could be blended with 0.35 parts of water to form an easily workable and mouldable paste which became firm after 6 minutes and set to a hard, dense mass soon after.

This material blended with 0.35 parts of a 0.5% potassium sulphate solution formed an easily workable and mouldable paste which became firm after 3 minutes, and set to a hard dense mass soon after.

Example 2

2 moles of analytical grade calcium carbonate was added slowly and with gentle agitation to 2L of 1N analytical grade sulphuric acid in a 3 litre glass beaker. When the effervescence has subsided and the pH of the resulting suspension was substantially neutral, pH = 7.0, the suspended mass in its container was heated in an autoclave to a temperature of 130°C and maintained at that temperature for 3 hours. After cooling, the precipitated calcium sulphate was allowed to soak in the supernatant for a period of 3 days and then all supernatant liquid was drained away. This powder was treated hydrothermally as in Example 1 above to produce an α hemi-hydrate.

Example 3

500 gms of the precipitated calcium sulphate di-hydrate from Example 1 were put into a glass beaker, which was placed in an oven at 200°C for 24 hours. On removal from the oven, 500 mls of 0.1% succinic acid solution were added to the beaker, ensuring that all of the powder was immersed. This was soaked for 16 hours, at which time the supernatant liquid was drained away to reveal a coarse textured recrystallised gypsum powder.

This powder was treated hydrothermally as in Example 1 above, followed by drying and crushing.

The resulting α hemi-hydrate was blended with 0.45 parts of water to form a paste which became firm after 6 minutes and set to a hard, dense mass soon after.

Example 4

500 gms of the precipitated calcium sulphate di-hydrate from Example 2 were calcined in an oven at 400°C for 2 hours. The anhydrite so formed was the orthorhombic or so called dead burned variety. This was removed from the oven, immersed in deionised water and allowed to soak for a period of 14 days. The supernatant liquid was drained away to reveal a coarse, gritty recrystallised

gypsum powder. This was hydrothermally treated in an autoclave for 2½ hours at 1.7 bar. The resulting α hemi-hydrate was dried at 110°C and crushed to pass a 125 micron mesh sieve. This gave a material which was blended with 0.38 parts of sterile, deionised water to form a mouldable paste which became firm 5 minutes after mixing, and set to a hard mass soon after.

Example 5

Recrystallised di-hydrate prepared according to Example 1 was dried at 40°C overnight. The dried material was crushed to pass a 150 micron mesh sieve and the resulting fine powder was heated in a shallow stainless steel tray at a depth of 2 cm for 2 hours at 165°C. The hemi-hydrate so formed was of the β variety, and was blended with 0.65 parts of sterile deionised water to form a mouldable paste which set to give a firm mass.

Example 6

500gms of the precipitated calcium sulphate di-hydrate from Example 1 were put into a glass beaker, which was placed in an oven at 150°C for 40 minutes. On removal from the oven, the resultant β hemi-hydrate was added to 600ml of deionised water and mixed to form a fluid mass. This was poured into a shallow stainless steel tray and allowed to re-hydrate and set. The following day the set gypsum in the stainless steel tray was put into an oven at 250°C for 20 hours to allow for complete dehydration. The resulting calcium sulphate anhydrite was covered with deionised water and allowed to soak for a period of 4 days and then all supernatant liquid was drained away to reveal a coarse textured recrystallised gypsum powder. This powder was treated hydrothermally as in Example 1 above to produce an α hemi-hydrate.

Summary

Examples 1 and 2 show alternative means of precipitating and subsequently dehydrating the initial calcium sulphate di-hydrate.

Example 4 shows that the insoluble anhydrite requires a much longer crystallisation time than the soluble variety. Example 5 shows the use of dry heat calcination to produce the β hemi-hydrate. It has been found that using a salt for the rehydration speeds up the process, as is illustrated in Example 3. Finely powdered gypsum may be added to act as crystal seeds.

Example 6 shows that the synthetic precipitated calcium sulphate di-hydrate can first be formed into a hemi-hydrate followed by re-hydration with a minimum quantity of water to form a set mass of di-hydrate. This set di-hydrate can then be dehydrated and recrystallised as previously described.

The above examples describe production of calcium sulphate hemi-hydrate which can be formed into a paste. The α hemi-hydrate thus formed can be blended with 0.30 to 0.40 parts water or saline solution to give a mouldable paste which sets to a firm mass. The β hemi-hydrate requires 0.55 to 0.70 parts water to form an appropriate paste.

If the calcium sulphate is required to be used in a pellet form, the calcination from the di-hydrate to the hemi-hydrate is not required. The subsequent di-hydrate would be ground or crushed and formed into pellets of an appropriate size.

There is thus described a method of producing surgical grade calcium sulphate which combines the advantages of the synthetic route with the characteristics encountered with naturally occurring gypsum. The method is relatively straightforward and can thus be readily reproduced, and without significant extra costs. The calcium sulphate produced by the methods herein described can provide an improved delivery means for the controlled release of medicaments into the body by virtue of their high chemical and phase purity compared to naturally occurring calcium sulphate. This provides for a more consistent and predictable rate of dissolution of the calcium sulphate and release of the medicament contained therein.

Various modifications may be made without departing from the scope of the invention. For example, the initial di-hydrate may be formed by neutralising lime with sulphuric acid. Other materials such as calcium chloride or sodium sulphate, may be used to form the initial calcium sulphate. Other salts may be used during the process as is required. Other conditions may be applicable to the dehydration, rehydration or calcining.

Whilst endeavouring in the foregoing specification to draw attention to those features of the invention believed to be of particular importance it should be understood that the Applicant claims protection in respect of any patentable feature or combination of features hereinbefore referred to and/or shown in the drawings whether or not particular emphasis has been placed thereon.

Claims

1. A method of producing surgical grade calcium sulphate characterised in that the method comprises forming an initial calcium sulphate di-hydrate from synthetic constituents; dehydrating the initial calcium sulphate di-hydrate to form calcium sulphate anhydrite; and subsequently rehydrating the calcium sulphate anhydrite and allowing subsequent calcium sulphate di-hydrate to crystallise out.
2. A method according to claim 1, characterised in that the subsequent di-hydrate is used as a solid material bone filler.
3. A method according to claims 1 or 2, characterised in that the subsequent di-hydrate is formed into pellets.
4. A method according to claim 3, characterised in that the crystallised subsequent calcium sulphate di-hydrate is ground prior to forming into pellets.
5. A method according to claim 1, characterised in that the subsequent calcium sulphate di-hydrate is calcined to form calcium sulphate hemi-hydrate.
6. A method according to claim 5, characterised in that the calcium sulphate hemi-hydrate is mixed with water to form a settable paste.
7. A method according to claim 5, characterised in that the calcium sulphate hemi-hydrate is mixed with a salt solution to form a settable paste.
8. A method according to any of claims 5 to 7, characterised in that the calcining is hydrothermal to form α calcium sulphate hemi-hydrate.
9. A method according to claim 8, characterised in that the calcining is carried out in an autoclave.

10. A method according to claim 9, characterised in that the calcining is carried out at a pressure of 1-6 bar.
11. A method according to claim 10, characterised in that the calcining is carried out at 2-3 bar.
12. A method according to any of claims 5 to 7, characterised in that the calcining is carried out in dry heat conditions.
13. A method according to claim 12, characterised in that the calcining is carried out at a temperature of 70 - 200°C.
14. A method according to claim 13, characterised in that the calcining is carried out at 150 - 175°C.
15. A method according to any of claims 8 to 14, characterised in that the calcining is carried out for a period of a half to six hours.
16. A method according to claim 15, characterised in that the calcining is carried out for one to two hours.
17. A method according to any of claims 5 to 15, characterised in that following calcining, the calcium sulphate hemi-hydrate is ground to a powder.
18. A method according to claim 17, characterised in that the powder has particle size of less than 150 microns.
19. A method according to any of the previous claims, characterised in that the initial calcium sulphate di-hydrate is formed by mixing soluble calcium and sulphate salts such that calcium sulphate precipitates out.
20. A method according to claim 19, characterised in that the initial di-hydrate thus formed is washed, and subsequently filtered, crushed and/or

dried.

21. A method according to claims 19 or 20, characterised in that the calcium salt is a chloride.
22. A method according to claims 19 or 20, characterised in that the calcium salt is a nitrate.
23. A method according to any of claims 19 to 22, characterised in that the sulphate is a sodium salt.
24. A method according to any of claims 19 to 22, characterised in that the sulphate is a potassium salt.
25. A method according to any of claims 19 to 22, characterised in that the sulphate is a ammonium salt.
26. A method according to any of claims 19 to 25, characterised in that the calcium and sulphate salts are provided in a substantially equal molecular ratio.
27. A method according to any of claims 1 to 18, characterised in that the initial calcium sulphate di-hydrate is formed from neutralising lime with sulphuric acid.
28. A method according to any of the previous claims, characterised in that the dehydration of the initial calcium sulphate di-hydrate takes place within a temperature range 110 - 350°C.
29. A method according to claim 28, characterised in that the dehydration of the initial calcium sulphate di-hydrate takes place at less than 300°C.
30. A method according to any of claims 1 to 27, characterised in that the dehydration of the initial calcium sulphate di-hydrate takes place at a

temperature above 350°C to form insoluble anhydrite.

31. A method according to claim 30, characterised in that the rehydration takes more than five days.
32. A method according to any of the preceding claims, characterised in that the dehydration of the initial calcium sulphate di-hydrate by the application of heat takes place in an open container.
33. A method according to any of claims 1 to 31, characterised in that the dehydration of the initial calcium sulphate di-hydrate by the application of heat takes place in a closed container.
34. A method according to any of the preceding claims, characterised in that the dehydration of the initial calcium sulphate di-hydrate by the application of heat takes place hydrothermally in the presence of steam.
35. A method according to any of the preceding claims, characterised in that the rehydration of the calcium sulphate anhydrite takes place immediately following dehydration.
36. A method according to any of the preceding claims, characterised in that the calcium sulphate anhydrite is fully immersed in water for rehydration.
37. A method according to any of claims 1 to 35, characterised in that the calcium sulphate anhydrite is fully immersed in a dilute salt solution for rehydration.
38. A method according to claim 37, characterised in that the salt solution comprises succinic acid.
39. A method according to claim 37, characterised in that the salt solution comprises potassium sulphate solution.

40. A method according to any of claims 37 to 39, characterised in that the concentration of the salt solution is less than 1%.
41. A method according to claim 40, characterised in that the concentration of the salt solution is substantially 0.1%.
42. A method according to any of the previous claims, characterised in that finely powdered calcium sulphate di-hydrate is added to be present during rehydration such that the powdered calcium sulphate acts as crystal seeds.
43. A method according to claim 42, characterised in that addition is in the order of 5g per litre of water.
44. A method according to claims 28 or 29, or any of claims 32 to 43 when dependent on claims 28 or 29, characterised in that the rehydration takes less than five days.
45. A method according to any of the preceding claims, characterised in that the subsequent calcium sulphate di-hydrate is dried following crystallisation.
46. A method according to claim 8, or any of claims 9 to 44 when dependent on claim 8, characterised in that the subsequent calcium sulphate di-hydrate is held in a damp condition prior to calcining.
47. Any novel subject matter or combination including novel subject matter disclosed herein, whether or not within the scope of or relating to the same invention as any of the preceding claims.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/02584

A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C01F A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y		<p>8-11, 35-44</p>
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Y	<p>US 4 360 386 A (BOUNINI LARBI) 23 November 1982 (1982-11-23) the whole document</p>	<p>35-44</p>
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Zalm, W

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

Interns 31 Application No

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